Session V. Vector insects and transmission of diseases

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Do we have to get rid of mosquitoes to eliminate malaria?

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Malaria is a local disease with global impact. The fitness of vector-borne *Plasmodium* parasites, the causative agents of malaria, is closely linked to the ecology and evolution of its mosquito vector. Ongoing adaptive radiation and introgression diversify mosquito populations in Africa. However, whether the genetic structure of vector populations impacts malaria transmission remains unknown.
We discuss below new approaches that gauge the contribution of mosquito species to *Plasmodium* abundance in nature, with a particular focus on time-series analyses in the context of population genetics and epidemiology [1]. Our data highlighted the importance of focusing vector control strategies on mosquito species that drive malaria dynamics.
Using time-series collections and the econometric approach Granger causality, we demonstrated that the abundance of *Plasmodium*-infected mosquitoes in a field site in Mali was driven by only one of the two sympatric vectors (Fig. 1). This mosquito species carried a susceptible allele of the known antiparasitic gene *TEP1* [2,3], and until now it was resistant to colonization efforts and, therefore, is not the target of current gene drive applications.
Extending such studies to other key components of vectorial capacity and epidemiological and parasitological surveys should ultimately identify patterns, tipping points, and general laws that describe dynamics, emergence, and resurgence of mosquito-borne diseases.

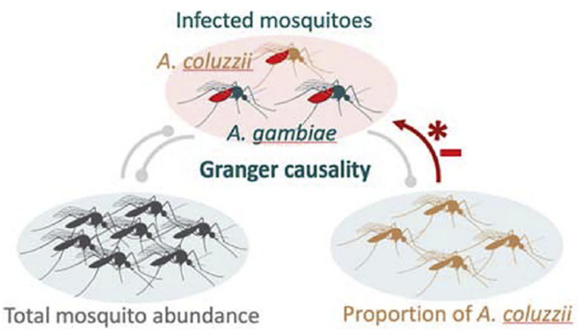

Fig. 1 Granger causality.

Disclosure of interest The authors declare that they have no competing interest.

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https://doi.org/10.1016/j.crvi.2019.09.022

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Human activities and climate change in the emergence of vector-borne diseases

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Because of human population expansion and activities, arthropod-borne viruses (arboviruses) have increased in importance during these last decades. Arboviruses are maintained by alternate replication in both vertebrate hosts and arthropod vectors. Successful transmission relies on a complex life cycle in the vector, which starts when a competent arthropod ingests an infectious blood meal from a viremic vertebrate host. Following an extrinsic incubation time during which the virus replicates in the vector midgut, followed by systemic viral dissemination to the salivary glands, the vector can transmit the virus to a new naïve host. Whereas they typically cause self-limiting, acute infections in their vertebrate hosts, arboviruses establish persistent infections in their vectors.
Arboviruses are typically maintained within an enzootic cycle between wild animals and vectors. As human populations encroach on regions where these diseases are endemic, spillover transmission to humans and domestic animals can lead to large-scale disease outbreaks affecting millions of people. Dengue, chikungunya, Zika, and yellow fever mainly use humans as amplification hosts. Extensive urbanization combined with increased commerce and travel give rise to the mosquitoes *Aedes aegypti* and *Aedes albopictus*, both highly adapted to the human environment. The high densities of these human-biting mosquitoes that proliferate in highly populated cities made the bed to explosive outbreaks of arboviral diseases. As insects are ectothermic organisms, climate change may affect the geographical distribution of vectors, with consequences on the transmission of arboviruses.
Yellow fever (YF) is a good example of an emerging arbovirus, as it illustrates three main steps in the emergence: (i) introduction of a new pathogen in a new environment causing urban outbreaks, (ii) spillback of this pathogen into the wild initiating an enzootic cycle, and (iii) the spillover of this pathogen from an enzootic cycle to initiate an urban cycle (Fig. 1).
YF (YFV, *Flavivirus*, Flaviviridae) is a disease endemic to tropical regions of Africa and South America. There are seven lineages: five in Africa and two in America. Each year, 200,000 cases and 30,000 deaths were reported. In 2016, YFV emerged in Angola and imported cases were detected outside Africa, posing the threat of emergence of this virus outside Africa and Americas (Amraoui et al. *Euro Surveill* 2016).
YFV was introduced into the New World during the slave trade, causing devastating outbreaks in several American countries, including cities like New York City and Boston. Once Carlos Finlay and Walter Reed had demonstrated that the YFV was transmitted by a mosquito, *Ae. aegypti*, eradication campaigns of the vector were initiated, leading to the control of YF.
In Brazil, *Ae. aegypti* was eradicated in 1954. YF disappeared from cities and only persisted in a sylvatic cycle where YFV circulated between zoophilic mosquitoes (*Hemagogus* and *Sabethes*) and non-human primates. Using experimental infections, we showed that the zoophilic mosquitoes (*Hemagogus leucocelaenus* and *Sabethes albiprivus*) were able to transmit YFV at very high rates (Couto-Lima et al. *Sci Rep* 2017). With the relaxation of control measures in Brazil, *Ae. aegypti* was reintroduced in 1967 and *Ae. albopictus* in 1986. We showed that *Ae. aegypti* and *Ae. albopictus* were highly susceptible to YFV. We also demonstrated that using a protocol of experi-

mental selection, we were able to select a YFV well adapted to a transmission by *Ae. albopictus* (Amraoui et al. *Sci Rep* 2018). This result should alert about the potential of YFV to initiate an urban cycle in Brazil, like in the past.

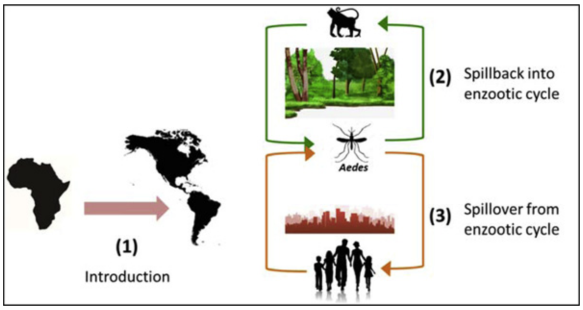

Fig. 1 The three main steps in the emergence of an arbovirus.

Disclosure of interest The author declares that she has no competing interest.

https://doi.org/10.1016/j.crvi.2019.09.023

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Benefits and limitations of emerging techniques for mosquito vector control

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In response to a broad governmental referral, the French High Council for Biotechnology has published an opinion on the use of genetically modified (GM) mosquitoes for vector control [1]. Emerging techniques of vector control were developed to overcome (i) the lack of therapies, preventive treatments and vaccines for most mosquito-borne diseases, and (ii) the limitations of existing vector control techniques (the situation is particularly critical regarding insecticides: in France, essentially only one insecticide is used against adult mosquitoes (deltamethrin), and its efficacy decreases due to resistance evolution in mosquito populations).

To date, only one GM mosquito-based technique has been developed to an operational level, Oxitec's RIDL technique, which seeks to reduce a mosquito population by repeated mass releases of sterilising transgenic males [2]. Two other techniques under development rely on CRISPR-based gene drive, seeking to spread a genetic trait in a wild population, either to eliminate the population by spreading sterility [3] or to make the target mosquitoes incapable of transmitting pathogens [4].

To identify the specific benefits and limitations of the different GM mosquito-based techniques, a cross-analysis of different vector control techniques was conducted with respect to possible objectives, efficacy and sustainability, technical constraints and risks to health and the environment. Consideration was given to both existing techniques (chemical, biological, physical, and environmental) and emerging techniques based on release of mosquitoes, whether GM (RIDL and the different gene drive techniques) or non-GM–irradiated (standard sterile insect technique (SIT)) or carrying *Wolbachia*[1] (incompatible insect technique (IIT) and spread of pathogen interference (PI) technique).

As specified by the referral, we considered the mosquito-borne diseases and vector species present across France, including overseas territories. The French territories being dispersed across the world, the most notable mosquito-borne diseases worldwide were considered, namely dengue, chikungunya, Zika, yellow fever, West Nile fever, for the viral diseases, and malaria and lymphatic filariasis for the parasitic diseases. We focused on the corresponding local vector species: mainly *Aedes aegypti* and *Aedes albopictus*, and species of Anopheles and Culex.

These vector species have very distinct features, not only in distribution and vector competence, but also in bio-ecology (reproduction modes, potential for survival, host preferences, peaks and sites of aggressiveness, invasive potential...). The vector systems themselves (the triad mosquito/pathogen/vertebrate host), as well as the diversity of situations encountered across the territories add another layer of complexity. This overall complexity must be understood and taken into account in order to design the most appropriate vector control strategy.

Cross-analysis of the different vector control techniques has been conducted in great detail and has made it possible to identify specific features and relative benefits and limitations of each of these techniques. Detailed results are developed in HCB's opinion (HCB, 2017).

At a more general level, we found:

– no divide between GM and non-GM techniques or between emerging and existing techniques (Fig. 1);

– shared characteristics within different sets of techniques, i.e. (i) techniques based on release of mosquitoes, (ii) population reduction techniques[2] vs. population modification techniques[3], (iii) self-limiting techniques[4] vs self-sustaining techniques[5];

– complementarity of the techniques.

Lastly, we found that the benefits and limitations of these vector control techniques cannot be treated in a generic manner, but will depend on the target vector species, the intended objective, and the broader context (epidemiological, environmental and socio-economic context, including available human and financial resources).

Key highlights for each of these broad conclusion points are developed below.

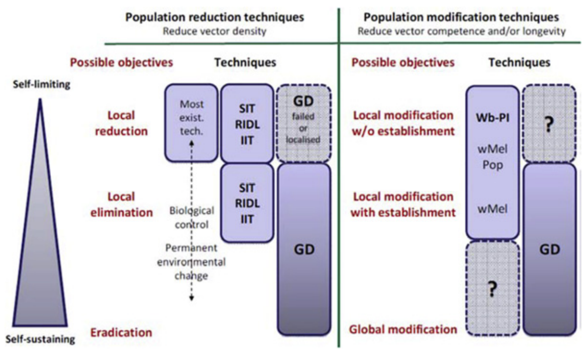

Fig. 1 Possible objectives and sustainability potential of existing and emerging vector control techniques (Insects Grand Conference Talk, C. Golstein and P. Boireau, 14 March 2019). Most exist. tech.: Most existing vector control techniques, including use of chemical insecticides; SIT: standard Sterile Insect Technique (mostly based on irradiated mosquitoes); RIDL: Release of Insects carrying a Dominant Lethal (GM-mosquito based technique); IIT: *Wolbachia*-mediated Incompatible Insect Technique; GD: Gene Drive techniques, for population elimination or modification (GM-mosquito based techniques in this report); Wb-PI: *Wolbachia*-mediated spread of pathogen interference; *w*Mel Pop and *w*Mel: two different strains of *Wolbachia*.